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ABSTRACT

The goals of the Advanced Cancer Detection Center include the discovery of molecular and genetic markers of cancer risk, the identification of individuals at high risk for cancer through screening and the testing of methods to prevent cancer. The Center also focuses on the development of new technologies for enhancing education and communication via web-based tool development. The projects included in this report are:

Lung Cancer Screening with Computed Tomography: Initial Results of Cohort Screening Trial

The Tampa Bay Ovarian Cancer Study

Development of the Moffitt Cancer Network

Epoxide Hydrolase Genetic Polymorphisms and Their Functional Significance

African American Families with Inherited Breast or Ovarian Cancer

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INTRODUCTION:

The **Advanced Cancer Detection Center** (ACDC) of the H. Lee Moffitt Cancer Center and Research Institute at the University of South Florida received initial funding in October 1997. In 2001, funding that was appropriated in FY00 and FY01 was awarded separately to the University of South Florida for the project period 2001-2006. This new award was made because several projects funded from the original award were still ongoing and funds in the original award were obligated to complete them. Those projects included:

Epoxide Hydrolase Genetic Polymorphisms and Their Functional Significance,

Automated Quantified Screening for Melanoma,

Breast Cancer Screening in High-Risk Women: Comparison of Magnetic Resonance Imaging (MRI) with Mammography, and

Adaptive Computer Assisted Diagnosis (CAD) Method for Lung Nodule Early Detection.

and were reported in the final report of DAMD17-98-1-8659. One project, *Development of the Moffitt Cancer Network*, continues beyond the earlier DoD grant and is included in annual progress reports for the current award, DAMD17-01-2-0056. As new projects are funded under the new initiative, their progress reports will also be included.

The ACDC has addressed the goals identified in its appropriations language through studies that target the discovery of molecular and genetic markers of cancer risk, the identification of individuals at high risk for cancer through screening, and the testing of methods to prevent cancer. In addition, the ACDC created a technology base that provides online video streaming, video supported web casting and teleconferencing and the development and application of expert systems. The success of these efforts has led to advances in cancer detection (publications) and the development of systems that have attracted additional peer-reviewed funding. The ACDC has received supplemental funding for a conference on molecular oncology and biomarkers which is still in its planning stages.

In order to accomplish the overall programmatic goals, the Advanced Cancer Detection Center supports research and demonstration projects that further its mission. Further, it has fostered projects that have extend the technologies developed into other settings and generalized the approaches to stimulate their application in several different directions. Preference is given to projects that extend system development and have the potential to lead to independent peer reviewed funding.

Additionally, this progress report contains progress on several projects previously funded under the auspices of the ACDC whose results are now coming to fruition and have resulted in important publications and presentations. The supported studies are:

Cad Vs. Human Accuracy in the Interpretation of Screening Mammograms: A Pilot Study (C Beam, PhD and W. Qian, PhD)

Lung Cancer Screening with Computed Tomography:Initial Results of Cohort Screening Trial (Robert A. Clark, M.D., Todd Hazelton, M.D., Lynn Coppage, M.D., Thomas N. Chirikos, Ph.D., Frank Walsh, M.D., Mark Rolfe, M.D., Lary Robinson, M.D., Eric Sommers, M.D., Nina R. Wadhwa, M.S.P.H., Gerold Bepler, M.D., Jeffrey Krischer, Ph.D., Melvyn Tockman, M.D., Ph.D).

BODY:

Overview: The H. Lee Cancer Moffitt Center & Research Institute includes a free standing patient care facility with a large inpatient and outpatient capacity, a major research institute consisting of more than 130 scientific members, a free standing Lifetime Cancer Screening Center and a wide array of outreach and educational activities for the general public and select underserved populations. Moffitt Cancer Center's location at the convergence of the University of South Florida's Health Sciences Center and the main campus sets the stage for its conceptual commitment to interdisciplinary approaches to research and patient care. Moreover, it allows the Center to enjoy all intellectual advantages of a matrix center while remaining operationally freestanding. After 18 years, the Cancer Center's mission remains totally focused on "contributing to the prevention and cure of cancer."

The Cancer Center was created by the Florida Legislature in the early 1980s, to meet a clear and compelling need to respond to Florida's "cancer epidemic." Building a major cancer research and treatment center at the University of South Florida in Tampa was largely the vision of H. Lee Moffitt, a state legislator who served as Speaker of the Florida House of Representatives from 1982-84. Construction of the original, 380,000 square foot hospital facility was funded with $70 million from the state's cigarette tax, allowing the Center to open in 1986.

The initial phase of the Cancer Center's strategic plan called for a rapid and substantial deployment of its clinical, financial, and philanthropic resources to develop a true scientific center of excellence. The Center recruited Dr. John C. Ruckdeschel as the Cancer Center's first director in late 1991. In 1992, he began fulfilling that strategic plan, a process that culminated in the awarding of a Cancer Center Support Grant (CCSG) five years later.

The strategic plan's second phase continues the focus on scientific and clinical growth, with a commitment to increase research facilities by over 200,000 sq.ft., and to prepare to accommodate twice as many patients by 2009. In 1998, the state legislature committed an additional $100 million to finance the construction needed to meet these goals.

In August, 2002, Dr. William Dalton was recruited to become the Cancer Center Director replacing Dr. Jack Ruckdeschel. Dr. Dalton was the Dean of the College of Medicine at the University of Arizona and previously was the Associate Center Director for Clinical

Investigations at the Moffitt Cancer Center for 5 years. Thus, Dr. Dalton brings to his new role a considerable experience in the operations of the Cancer Center and an in-depth background in the development of the Cancer Center's scientific agenda.

In April, 2003, Dr. Krischer stepped down as program leader for the Cancer Control Program and returned to the faculty to focus on research. Dr. Thomas Sellers was recruited from Mayo Clinic to be the Associate Center Director for Cancer Control and the new program leader. Dr. Krischer continues to be an active member of the Cancer Control Program with extensive collaborations in Cancer Control and in the Experimental Therapeutics Program. In the latter program, new projects apply molecular markers to investigations of the natural history of disease leading from benign to malignant and also mechanistic studies that can lead to a better understanding of the underlying disease process. For several of these projects, funding is being sought external to the ACDC since they involve both clinical and laboratory studies.

Today, the Cancer Center's membership numbers 150 scientists and clinicians who are USF faculty. A new collaborative agreement is in place between the Cancer Center and the University extending the availability of core facilities and promoting collaborative research. More than 94 members-in-residence are housed and supported in the Center's facilities and work under the terms of the USF/Moffitt affiliation and faculty support agreements. Other members are based in University departments. All are USF faculty. The Cancer Center's 1,500 employees support the work of the physicians and scientists. The Center has annual operating revenues of over $130 million yearly, including an $11 million annual appropriation from the State of Florida, research grants totaling more than $36 million overall (direct), philanthropic donations, and institutional commitment from the University of South Florida in the form of faculty salaries and a portion of clinical practice revenues.

The Cancer Center currently supports four scientific programs: Molecular Oncology, Immunology, Clinical Investigations, and Cancer Control. The Cancer Control Program consists of two subprograms: cancer prevention and health outcomes and behavior. Dr. Krischer's research activities are programmatically aligned with the health outcomes and behavior subprogram. A number of faculty are active collaborators in Dr. Krischer's program. They include:

Dr. Dmitry Goldgof, Associate Professor, Computer Science and Engineering, College of Engineering
Dr. Pamela Munster, Assistant Professor, Department of Interdisciplinary Oncology, College of Medicine
Dr. Rebecca Sutphen, Associate Professor, Department of Interdisciplinary Oncology, College of Medicine
Dr. Nagi Kumar, Associate Professor, Department of Interdisciplinary Oncology, College of Medicine
Dr. Paul Jacobsen, Professor, Department of Psychology, College of Arts and Sciences
Dr. Jennifer Mayer, Associate Professor, Department of Pediatrics, College of Medicine
Dr. Larry Hall, Professor, Computer Science and Engineering, College of Engineering

Dr. Cynthia Myers, Assistant Professor, Department of Interdisciplinary Oncology, College of Medicine
Dr. Rachel Richesson, Assistant Professor, Department of Pediatrics, College of Medicine

Additional collaborations have been developed with members of the Clinical Investigations Program:

Dr. Alan List, Professor, Department of Interdisciplinary Oncology, College of Medicine
Dr. P.K. Burnett, Assistant Professor, Department of Interdisciplinary Oncology, College of Medicine

These faculty members participate in ACDC projects or contribute to other research initiatives of Dr. Krischer's group with funding from multiple peer-reviewed sources. The successful competition for these funds has permitted the development of multiple research studies and a technology advanced infrastructure that supports them.

The funding of the Advanced Cancer Detection Center is one of three mechanisms by which this has occurred.

Advanced Cancer Detection Center

The Advanced Cancer Detection Center has become a significant component of the infrastructure in that it provides a stimulus for research development and promotes inter and intra programmatic collaborations. The Advanced Cancer Detection Center supports pilot studies that can lead to peer-reviewed extramural funding. Projects supported by this mechanism follow a two-tiered scientific review process in which the science and the likelihood of peer-reviewed extramural funding are considered. In addition, priority is given to projects that foster inter and intra-programmatic collaborations.

Recognizing the great success of this effort, the focus of the Advanced Cancer Detection Center has worked to complement the other infrastructure mechanisms in most notably the Community Clinical Oncology Program Research Base (described below). That program also provides funds for pilot studies. This has led to the consolidation of the internal advisory committee for each program so that there is continuity between programs. The membership of the consolidated internal advisory committee includes some members from the existing Advanced Cancer Detection Center advisory committee as well as leaders of the Community Clinical Oncology Program Research Base. For 2004-05, the members are:

Dr. Pamela Munster, Assistant Professor, Department of Interdisciplinary Oncology, College of Medicine
Dr. Nagi Kumar, Associate Professor, Department of Interdisciplinary Oncology, College of Medicine
Dr. Rebecca Sutphen, Associate Professor, Department of Interdisciplinary Oncology, College of Medicine
Dr. Jennifer Mayer, Assistant Professor, Department of Pediatrics, College of Medicine

Dr. Susan McMillan, Professor, College of Nursing.
Dr. Jeffrey Krischer, ex officio, Professor, Department of Pediatrics, College of Medicine

These members reflect expertise in genetics, nutrition, behavioral science, endocrinology, oncology, pediatrics and epidemiology. Some have been the principal investigators of studies that have previously received Advanced Cancer Detection Center support and all have experience in obtaining peer-reviewed research support.

Moffitt CCOP Research Base (PI:Krischer)

The H. Lee Moffitt Cancer Center received funding by the NCI in June 2000, and refunded in 2005, to develop a research base as a mechanism for Community Clinical Oncology Programs to access cancer control clinical trials. NCI funded CCOPs, direct affiliates and Moffitt affiliates are eligible to participate in the Moffitt CCOP Research Base. Membership is based on continued funding as an NCI CCOP with satisfactory performance measured by accrual and data quality.

The goals of the Moffitt CCOP Research Base are to:

- Develop cancer control trials of high scientific merit for implementation in the community setting.
- Provide community investigators an opportunity to participate in NCI-supported cancer control clinical trials.

The following CCOPs have, or are in the process of, establishing formal affiliations with the Moffitt CCOP research base:
Florida Pediatric CCOP, Tampa, FL
Merit Care Hospital CCOP, Fargo, ND
Mount Sinai Medical Center CCOP, Miami, FL
South Texas Pediatric MBCCOP, San Antonio, TX
Baptist Center Research Institute CCOP, Memphis, TN
Cancer Research for the Ozarks CCOP, Springfield, MO
Columbus CCOP, Columbus, OH
Greater Phoenix CCOP, Phoenix, AZ
North Shore University Hospital CCOP, Manhassett, NY
NorthWest CCOP, Boise, ID
Southern Nevada Cancer Research Foundation CCOP, Las Vegas, NV

The Moffitt CCOP Research Base is now staffed and cancer control protocols and concepts are being initiated. Several of the clinical studies are the result of pilot development funded by ACDC projects. All are approved by the internal advisory committee and then reviewed and approved by the National Cancer Center before activation. The National Cancer Center, Division of Cancer Prevention provides the scientific review for all clinical studies conducted under this mechanism after review by ACDC leadership and recommendations to support the studies. Examples of current studies are:

The Specific Role of Isoflavones in Reducing Prostate Cancer Risk	Protocol

A Randomized Pilot Clinical Trial of the Action of Isoflavones and Lycopene in Localized Prostate Cancer: Administration Prior to Radical Prostatectomy.	Protocol
The Effect of Cyproheptadine (periactin) and Megestrol Acetate (Megace) on Weight in Children with Cancer/Treatment Related Cachexia	Protocol
Adderall-XR Versus Concerta for Cancer Treatment-Related Neurocognitive Sequellae and Depression in Pediatric Patients: A Randomized Phase II Study.	Protocol
Stress Management Training for Patients Undergoing Radiotherapy	Protocol
Oral Glutamic Acid to Decrease Vincristine Toxicity in Children with Cancer	Concept
Preservation of Ovarian Function in Young Women Treated with Neoadjuvant Chemotherapy for Breast Cancer: A Randomized Trial Using the GnRH Agonist (Triptorelin) During Adjuvant Chemotherapy	Protocol

Data and Technology Coordinating Center, Rare Diseases Clinical Research Network

To address the challenges inherent in diagnosing and treating rare diseases, the National Institutes of Health (NIH) created the Rare Diseases Clinical Research Network. With $51 million in grant funding over five years from several NIH components, the network will consist of ten Rare Diseases Clinical Research Centers (RDCRCs) and a Data and Technology Coordinating Center (DTCC).

The RDCRCs and the DTCC are located at the following institutions:

-- Baylor College of Medicine, Houston, TX - Rare Disease Clinical Research Center for New Therapies and New Diagnostics - Dr. Arthur L. Beaudet

-- Boston University School of Medicine, Boston, MA - Vasculitis Clinical Research Network - Dr. Peter A. Merkel

-- Children's Hospital Medical Center, Cincinnati, OH - Rare Lung Diseases Clinical Research Network - Dr. Bruce C. Trapnell

-- Children's National Medical Center, Washington, DC - Rare Diseases Clinical Research Center for Urea Cycle Disorders - Dr. Mark L. Batshaw

-- The Cleveland Clinic Foundation, Cleveland, OH - Bone Marrow Failure Clinical Research Center - Dr. Jaroslaw P.Maciejewski

-- University of Rochester, Rochester, NY - Nervous System Channelopathies Pathogenesis and Treatment - Dr. Robert C.Griggs

-- The Mount Sinai School of Medicine, New York, NY - The Natural History of Rare Genetic Steroid Disorders - Dr. Maria I. New

-- University of Colorado Health Sciences Center, Denver Colorado - Cholestatic Liver Disease Consortium - Dr. Ronald Sokol

-- University of North Carolina, Chapel Hill, North Carolina - Genetic Diseases of Mucociliary Clearance Consortium - Dr. Michael Knowles

-- Duke University - Rare Thrombotic Disease Clinical Research Consortium - Dr. Thomas Ortel

-- University of South Florida and the H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL - The Data and Technology Coordinating Center - Dr. Jeffrey P. Krischer

Approximately 25 million people in the United States are affected by an estimated 6,000 rare diseases or conditions. Diseases to be studied in the centers include: urea cycle disorders; Angelman's syndrome; Prader-Willi syndrome; Rett syndrome; periodic paralysis; non-dystrophic myotonic disorders; episodic ataxia; aplastic anemia; paroxysmal nocturnal hemoglobinuria; single lineage cytopenias, including granular lymphocyte leukemia, pure red cell aplasia, and myelodysplastic syndromes; vasculitis disorders; inborn defects in steroid hormone pathways; alpha-1 antitrypsin deficiency; lymphangioleiomyomatosis; pulmonary alveolar proteinosis; and hereditary idiopathic pulmonary fibrosis.

With a collaborative approach, the network will focus on identifying biomarkers for disease risk, disease severity and activity, and clinical outcome, while encouraging development of new approaches to the diagnosis, prevention, and treatment of rare diseases.

The network will facilitate increased collaboration and data sharing between investigators and patient support groups working to improve the lives of those affected by these diseases and potentially prevent or eliminate these diseases in the future.

This network supports the re-engineering of the clinical research enterprise component presented recently in the "Roadmap for Medical Research" by Dr. Zerhouni, NIH Director. Each research center consists of a consortium of clinical investigators partnering with patient support groups and institutions within and outside of the United

States that have agreed to work together studying a group of rare diseases. In addition to fostering collaborative research, the RDCRCs will train new investigators for the represented rare diseases and provide content for a public Web site on rare diseases research.

Integration of various kinds of data including genetic, microarray, clinical, laboratory, and imaging, is one of the goals of this informatics approach to clinical research being pursued at the University of South Florida. The RDCRCs and their sites will work with the DTCC in developing common data elements, data standards, and data structures. The DTCC will incorporate new approaches to data sharing and federated databases at distributed sites that are scaleable or have the potential for future expansion and adaptation. This approach will enable researchers to integrate data with other clinical networks such as the National Electronic Clinical Trials and Research (NECTAR) network.

Each RDCRC will utilize the resources available at the General Clinical Research Centers -- 82 facilities distributed across the United States that provide clinical investigators with specialized research environments and specially trained research personnel. Supported by NCRR, the facilities include nursing staff, research subject advocates, and various core technologies, including sophisticated laboratories, nutrition staff, and imaging facilities.

The Moffitt Cancer Center and Research Institute is one of the clinical sites of the RDCRN through its affiliation with the Bone Marrow Failure Consortium, based at Cleveland Clinic and through its close association with the Data Technology and Coordinating Center. Drs. Alan List and P.K. Burnette have been collaborating with Dr. Krischer on several new projects and applications for additional funding. The ACDC infrastructure is leveraged to support these studies and the laboratory studies are externally funded. Dr. Krischer has also participated in the development of several individual grant applications and protocols submitted to the protocol review committee of the Rare Diseases Network. Scientific review is provided by the grant review bodies and the Rare Diseases Network.

Drs. Rachel Richesson (Informaticist), Larry Hall (Professor of Computer Science) and Jeffrey Krischer all receive support from this funding mechanism which further enhances the technology infrastructure that has been built.

In fiscal year 2006, the Advanced Cancer Detection Center will further develop its Telemedicine and Informatics initiatives as a means to further its education objectives contained in enabling legislation. Those technologies already developed as part of the ongoing Moffitt Cancer Network will be expanded to other venues and further developed to achieve the following objectives:

Task 1: Develop and implement Pediatric Internet Telemedicine Homecare study to assess efficacy of low bandwidth monitoring, management and treatment in the care of childhood chronic diseases.

In conjunction with All Children's Hospital in St. Petersburg, Florida and the University of South Florida Department of Pediatrics we plan to expand the low-bandwidth video streaming capability developed under the Moffitt Cancer Network project to implement a pediatric telemedicine homecare study to assess efficacy of this technology. We hypothesize the use of general monitoring and management devices can greatly improve the transfer of accurate information about the patient's condition to the physician as well as provide the physician a window inside the patient home to evaluate various complications of his or her disease. We believe the heightened amount of accurate information in addition to remote access to care will improve the ability of the physician and caregiver to care for the patient resulting in overall better care. We will link the various settings of the Department (Tampa General Hospital, clinics at 17 Davis Island, USF Medical Center, the Children's Research Institute, St. Petersburg, and other clinical locations to provide the foundation for the extension of this technology. This extension of infrastructure will also provide more effective linkages between faculty of the ACDC (e.g., Dr. Jennifer Mayer located in Sarasota) who are in different geographical settings to coordinate leadership roles under the ACDC organizational structure.

Task 2: Develop and implement proof of concept study for genetic counseling delivered from a distance via telemedicine in a multi-center environment.

In conjunction with the Florida Cancer Genetics Network (FCGN), a network of eleven sites providing genetic counseling throughout the state of Florida, we plan to implement a proof of concept study for delivering genetic counseling via telemedicine in a multi-institutional environment. The FCGN is based at the Moffitt Cancer Center and was developed initially under Advanced Cancer Detection Center funding. The Genetics program at the Moffitt Cancer Center recently concluded a proof of concept for genetic counseling via telemedicine that showed promising results. The proof of concept was designed in such a way as to assess the technology as well as the patient and counselor's resistance to or acceptance of the delivery mode. The patient and counselor were physically located in the same building, although the encounter took place via telemedicine with the use of audio and videoconferencing software.

We developed the first internet-based system for cancer genetics risk assessment, genetic counseling and research registry participation. The system automates collection of the family and personal medical history information required for these processes. Data may be 1) entered online or 2) entered on paper forms that can be faxed into a web server for direct (automated) data entry accomplished within minutes. Once entered, data is available for viewing, editing and printing via a secure website. The system generates a family pedigree and risk calculation that can also be viewed or printed from the website. For research initiatives, data in the system can easily be queried to determine the number of individuals available who meet specific eligibility requirements. Authentication and authorization features allow easy access to all data for which the user has permission, while restricting all other data from access. Web access to the system requires a standard web browser (such as Microsoft Internet Explorer version 5.5 or higher) and use of free encryption software available on the internet. The system has two main uses – 1) it automates the data collection, pedigree-drawing and risk assessment procedures of

clinical genetic counseling for hereditary cancer susceptibility quickly and easily and 2) it facilitates enrollment of individuals with high cancer risk in a registry designed for individuals who are interested in participating in cancer research studies. The internet-based design of this system makes it accessible to cancer genetics centers around the world.

We propose to extend the scope of the study mentioned above to include multiple centers as well to assess efficacy using well defined tools to detect differences in knowledge transfer and patient outcomes relating to overall state of mind post counseling. This extends the current capabilities of the Cancer Network to make scarce resources more widely available to targeted populations and health care providers. In addition, we are exploring the extension of this effort to include pediatric genetics screening and counseling and have developed an extension for neurofibromatosis, which is a programmatic initiative of the DoD.

Task 3: Develop and implement an interactive intelligence search and representation system for mining disease information to aid in proper diagnosis.

The system that will be built is a dynamic, self-organizing network of information that will adapt to user needs. When completed, this system will model the data, use machine learning to adapt its' own search mechanisms, store its own statistics, be scalable and 100% dynamic. It will also combine web presentation technologies with analytical systems, require initial education, and be classification and utilization based. There will be a way to add new information into the system and a way to change how the system learns.

The completed system will dynamically create web pages that display the data that the user has interest in. It will base its choices on the user's current path and statistical information about relationships or links between topics. Each user will be able to take a completely different path through the information and find completely different information in the same amount of time.

The more general statement of the problem is to semantically define relationships among granular data elements that reflect a structure imposed on the data by the user. This is equivalent to representing data in a structure such that the user can find related elements without having to know, a priori, the data structure. For example, to be successful in finding a folder that has been filed, the user might be better off knowing the filing system that determines whether the folder has been placed. The filing system might be alphabetical order, subject order, or some other ordering approach. If the filing system is organized by subject, then the user might have to know which is the most closely related subject heading for the file being sought. Yet, the user might have no awareness of how subjects are defined or even named. Similarly, if the task is to retrieve related files, then alphabetical ordering systems provide limited relational groups as compared to subject order filing systems, as long as the definition of the subject groups is explicit. Taken more generally, both data structures require the user to understand the data structure to be successful in any given query. This research will focus on more general data structures

that encode relationships and do not require the user to have any prior knowledge. We will explore the application of this approach to the design and construction of web pages, in the context of the Cancer Network, although the problem is much more general.

The underlying informatics approach will be developed by Dr. Rachel Richesson who is a trained inforaticist in collaboration with other faculty at USF. She is also developing a parallel study to be submitted to the National Library of Medicine for extramural funding.

Task 4: Upgrade existing hardware and server environment to replace aging equipment and maintain a state-of-the-art data and informatics infrastructure.

The ACDC, in the coming year, will continue to replace outdated equipment as well as add new technologies that foster new research. The primary network infrastructure will consist of a gigabit switched network connected to Internet2 through redundant sonic wall firewalls. Backup and storage systems are also being upgraded. The current version of Netbackup (running on Sun Solaris) has been purchased in conjunction with an ADIC LTO2 Tape library. This will aid significantly to ensuring enterprise backups are secure and reliable. The tape library and Netbackup system will be connected to an upgraded Fiber Channel 2 Storage Area Network (SAN).

The Storage Area Network consists of redundant FC2 McData Switches and two EMC CX300 Fibrechannel arrays in a RAID 5 configuration. Each machine will connect redundantly to the SAN and be allocated space on an as needed basis. Netbackup and the tape array mentioned above are connected directly to the SAN and backups will be done directly over the high speed SAN when possible. This greatly increases our ability to adjust rapidly to surges in demand of storage so common in today's IT world.

Upgraded Oracle production and development servers have been purchased and are being installed. Upgraded versions of Oracle have been secured as well. Once installation of the new system is complete, the existing database environment will be migrated from the outdate servers to the new ones. Sun V280Rs have been purchased to house Oracle.

Upgraded SAS production and development servers have been purchased and are being installed. The new Sun V240s will provide a significant improvement in analysis times.

Primary and Backup Domain Controllers are being upgraded to new Dell Poweredge 2650s and Window 2003. This will allow us to utilize updates to active directory and the new security measures within Windows 2003. Exchange 2003 is being implemented in concert with the upgrade of the domain controllers.

Web production, certification, and development servers are being upgraded. With the ever increasing influx of .Net technologies and the subsequent integration of the technologies into Windows 2003 it is prudent to upgrade the machines and migrate to Windows 2003. The tight integration of 2003 and .Net will ease development while improving programmatic efficiency and reducing development time.

A number of additional systems are being upgraded in conjunction with the systems mentioned above. The systems being upgraded are out of date for the applications they are running and/or the applications themselves are to be updated. These include, but are not limited to, the online automated pedigree system, the Automated Patient Response system which allows phone based randomization to clinical trials, and teleforms which allows automated fax in data collection for a number of ACDC projects.

A remote site will be setup at All Childrens Hospital Pediatric Genetics Department when space is available and a VPN tunnel setup to ride over the existing USF-Tampa to USF-St Pete ATM network.

The infrastructure upgrade currently taking place is a critical part of the further development of the network. The network continues to be a test bed of new technologies that foster and enhance research. Much has been accomplished in 2004-05. Yet additional work remains to be done. With the global changes in weather and the need for more secure, uninterruptible systems, we have begun to develop more extensive backup plans, including assessing the need for alternative power sources, hot back up facilities and off site (and out of state) back up storage and the ability to restore operations.

KEY RESEARCH ACCOMPLISHMENTS:

The material that follows in this section summarizes the key research accomplishments associated with each project and task outlined in the appropriate approved Statement of Work for ACDC approved projects during the previous year.

•Lung Cancer Screening with Computed Tomography: Initial Results of Cohort Screening Trial.
(Robert A. Clark, M.D., Todd Hazelton, M.D., Lynn Coppage, M.D., Thomas N. Chirikos, Ph.D., Frank Walsh, M.D., Mark Rolfe, M.D., Lary Robinson, M.D., Eric Sommers, M.D., Nina R. Wadhwa, M.S.P.H., Gerold Bepler, M.D., Jeffrey Krischer, Ph.D., Melvyn Tockman, M.D., Ph.D).

Recent publications:

A Systematic Review and Lessons Learned From Early Lung Cancer Detection Trials Using Low-Dose Computed Tomography of the Chest. *Gerold Bepler, MD, PhD, Dawn Goodridge Carney, MSPH, Benjamin Djulbegovic, MD, PhD, Robert A. Clark, MD, MBA, and Melvyn Tockman, MD, PhD*

Background: Computed tomography (CT) screening of the chest has shown promise for early detection of lung cancer, but evidence for a reduction in lung cancer mortality by CT screening is not available.
Methods: We reviewed 208 articles to synthesize available evidence for efficacy of CT screening in detecting potentially curative stages of lung cancer and for evidence in reducing lung cancer mortality. Other outcomes of interest included detection rate of cancer and of suspicious lesions, histology and stage of cancer at detection,

screening-related morbidity, and the identification of populations uniquely suited for CT screening. We identified eight papers that reported the outcomes for CT of the chest in lung cancer screening.
Results: Since none of the studies utilized a control group, quantitative pooling was not done. In two studies, both CT and chest radiography (CXR) were used as screening tools in the same cohorts. A total of 19,107 subjects were screened using CT. The detected prevalence rate for lung cancer ranged from 0.40% to 13.6% and was a function of the subjects' age and smoking history. CT screening resulted in a 3-fold higher detection rate and a 5-fold increase in the rate of resectable cancers compared to CXR. Data on lung cancer and overall mortality and screening-related morbidity and mortality were incomplete. CT screening resulted in selective detection of adenocarcinomas with an approximately 2- to 3-fold oversampling of this histologic subtype. The positive predictive value of CT screening was highest for subjects in the 8th decade of life, and it was virtually nil for those in their 5th decade.
Conclusions: Evidence regarding lung cancer screening by CT shows that this technology detects earlier-stage and smaller lung cancers with greater frequency than other screening methods. To date, no trials have demonstrated that CT screening leads to a reduction in lung cancer mortality. Until mortality trials are completed, low-dose CT screening should be considered an investigative tool rather than the standard of care.

Cancer Control 4:306-314, 2003.

Improbable Estimate of Lung Cancer Mortality From Screening Trials. *Melvyn S. Tockman, MD, PhD, H. Lee Moffitt Cancer Center, Tampa, FL*

To the Editor:

The recent article by Patz et al[1] titled "Estimate of Lung Cancer Mortality from Low-Dose Spiral Computed Tomography Screening Trials: Implications for Current Mass Screening Recommendations" addresses the important question whether helical computed tomography (CT) screening, detection, and intervention might be projected to reduce lung cancer mortality. In the absence of mortality data from the ongoing CT trials, the authors make several assumptions and adopt methods that lead to improbable projections of lung cancer mortality rates for two current CT screening trials (4.1 deaths per 1,000 person-years from the Mayo Clinic study[2]; 5.5 deaths per 1,000 person-years from Early Lung Cancer Action Project[3] [ELCAP]/Cornell[4]) that exceed the mortality in the usual care arm of the Mayo trial observed 30 years ago[5] (3.9 deaths per 1,000 person-years). These high mortality projections come from the application of the Mountain stage-specific survival rates to the cancers detected by helical screening, and then adding the "usual care" mortality (a nonstandard method).

Also, the authors do not discuss one of the most interesting features of their data. The CT trials at Mayo and Cornell seem to have detected a lung cancer–stage shift. Thirty years ago, the Mayo investigators removed the cancers detected at the first (prevalence) screen to calculate their incidence (new cancer) rate. The Mayo Lung Project–screened group found 5.5 new cancers per 1,000 person-years while the usual care group experienced 4.3 new cancers per 1,000 person-years. The current Mayo CT trial found 9.2 new cancers per 1,000 person-years, and the ELCAP trial found 9.6 new cancers per 1,000 person-

years. Thus, CT screening detected almost twice the number of new cancers, but projected only a similar to slightly higher mortality rate compared with the old Mayo trial. Some might suggest that not all the CT-detected lung cancers would actually be fatal (overdiagnosis). Nevertheless, Patz et al counted all of the new cases when calculating the expected mortality.

Of greater interest is the fall in the rate of advanced cancers detected. The old Mayo study detected 3.2 stage III unresected lung cancers per 1,000 person-years (incidence rates were 0.00316 in screened, 0.00325 in usual care). In contrast, Patz et al reports that the current Mayo CT study found 1.1 new advanced stage cancers per 1,000 person-years (five stage III/IV per 4,326 person-years) while ELCAP found 0.9 new advanced stage cancers per 1,000 person-years (two stage III/IV per 2,177 person-years). While there is controversy over the merit of finding additional early-stage cases of cancer, there is little doubt about the importance of finding fewer advanced cases after multiple years of follow-up.

In summary, modeling is often presented to estimate answers in the absence of data. Nevertheless, improbable results and nonstandard methods (ie, reporting the combined usual care mortality plus CT screened group mortality as screened group mortality) and discrepancies in Table 5 of the Patz et al article (stage distributions do not add to yearly totals) suggest that this report may not be the optimal model to project the lung cancer mortality reduction of helical CT screening.

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2. Swenson SJ, Jeh JR, Hartman TE, et al: Lung cancer screening with CT: Mayo Clinic experience. Radiology 226:756-761, 2003

3. Henschke CI, Naidich DP, Yankelevitz DF, et al: Early Lung Cancer Action Project: Initial findings on repeat screenings. Cancer 92:153-159, 2001

4. Henschke CI: Early Lung Cancer Action Project: Overall design and findings from baseline screening. Cancer 89:2474-2482, 2000 (suppl 11)

5. Fontana RS, Sanderson DR, Woolner LB, et al: Screening for lung cancer: A critique of the Mayo Lung Project. Cancer 67:1155-1164, 1991 (suppl 4)

Journal of Clinical Oncology, Vol 23, No 9 (March 20), 2005: pp. 2106-a-2107

•<u>The Tampa Bay Ovarian Cancer Study</u>

(Rebecca Sutphen, MD, Jeffrey Krischer, Ph D)

Recent publications:

Lysophospholipids are Potential Biomarkers of Ovarian Cancer. *Sutphen R, Xu Y, Wilbanks GD, Fiorica J, Grendys EC Jr, LaPolla JP, Arango H, Hoffman MS, Martino M, Wakeley K, Griffin D, Blanco RW, Cantor AB, Xiao YJ, Krischer JP.*
Department of Interdisciplinary Oncology, College of Medicine and H. Lee Moffitt Cancer Center and Research Institute, University of South Florida, Tampa, 33612, USA. rsutphen@hsc.usf.edu

OBJECTIVE: To determine whether lysophosphatidic acid (LPA) and other lysophospholipids (LPL) are useful markers for diagnosis and/or prognosis of ovarian cancer in a controlled setting. METHOD: Plasma samples were collected from ovarian cancer patients and healthy control women in Hillsborough and Pinellas counties, Florida, and processed at the University of South Florida H. Lee Moffitt Cancer Center and Research Institute (Moffitt). Case patients with epithelial ovarian cancer (n = 117) and healthy control subjects (n = 27) participated in the study. Blinded LPL analysis, including 23 individual LPL species, was performed at the Cleveland Clinic Foundation using an electrospray ionization mass spectrometry-based method. LPL levels were transmitted to Moffitt, where clinical data were reviewed and statistical analyses were performed. RESULTS: There were statistically significant differences between preoperative case samples (n = 45) and control samples (n = 27) in the mean levels of total LPA, total lysophosphatidylinositol (LPI), sphingosine-1-phosphate (S1P), and individual LPA species as well as the combination of several LPL species. The combination of 16:0-LPA and 20:4-LPA yielded the best discrimination between preoperative case samples and control samples, with 93.1% correct classification, 91.1% sensitivity, and 96.3% specificity. In 22 cases with both preoperative and postoperative samples, the postoperative levels of several LPL, including S1P, total LPA, and lysophosphatidylcholine (LPC) levels and some individual species of LPA and LPC, were significantly different from preoperative levels. CONCLUSION: LPA, LPI, LPC, and S1P appear useful as diagnostic and prognostic biomarkers of ovarian cancer

Cancer Epidemiol Biomarkers Prev. 2004 Jul;13(7):1185-91.

•<u>Development of the Moffitt Cancer Network</u>

(Jeffrey Krischer, Ph.D., Dmitry Goldgof, Ph.D., Larry Hall, Ph. D., Rachel Richesson, Ph.D.)

The technology of the Moffitt Cancer Network has been extended and implemented multiple new settings. An application has been developed for the Rare Diseases Clinical Research Network and the Community Clinical Oncology Research Base, as described above. In each application we have used the technology to implement online teaching methods using streaming video (e.g., the CCOP Research Base) and the use of web-based video conferencing (The RDCRN). A media center has been created for each of these applications to extend our previous work and focus on making the technology more generalizable. The media center concept has been expanded to provide a mechanism to certify the training of staff for clinical studies. The application facilitates

off site training in that embedded codes are used and recorded to verify that a trainee has been exposed to the material and can be certified for its content. This approach has been accepted by the ACGME for continuing education credits and has been adapted for training certification on clinical studies.

During the preceding year, we have begun the planning for upgrading the systems and replacing aging equipment to remain technologically current. We plan to complete the re-engineering of the network, with extensions to include the advances in telegenetics, and enhanced back-up facilities in the coming year as described above.

•**Epoxide hydrolase genetic polymorphisms and their functional significance.**
(Jong Y. Park, PhD)

Recent publications:

Genetic Analysis of Microsomal Epoxide Hydrolase Gene and its Association with Lung Cancer Risk. *Park JY, Chen L, Elahi A, Lazarus P, Tockman MS.,* Division of Cancer Prevention and Control, 12902 Magnolia Drive, H Lee Moffitt Cancer Center and Research Institute, Tampa, FL 33612, USA. parkj@moffitt.usf.edu

The human microsomal epoxide hydrolase (EH) gene contains polymorphic alleles, which may be linked to increased risk for tobacco-related lung cancer. The purpose of this study is to screen new polymorphisms and determine whether these polymorphisms can be used to predict individual susceptibility to lung cancer. The polymerase chain reaction-single strand conformation polymorphism (PCR-SSCP) analysis was used to screen for polymorphisms in the coding region of the EH gene. Eleven polymorphisms, including previously reported polymorphisms, were identified and the prevalence of these variants was assessed in at least 50 healthy Caucasians and African-Americans. Among the 11 polymorphisms, the prevalence of the amino acid-changing EH polymorphisms in codons 43, 113 and 139 was examined in 182 Caucasian incident cases with primary lung cancer, as well as in 365 frequency-matched controls to examine the role of EH polymorphisms in lung cancer risk. A significant increase in lung cancer risk was observed for predicted high EH activity genotypes (odds ratio (OR) 2.3, 95% confidence interval (CI) 1.2-4.3) as compared with low EH activity genotypes. This association was more pronounced among patients with lung adenocarcinoma (OR 4.7, 95% CI 1.7-13.1). These results suggest that the EH polymorphism plays an important role in lung cancer risk and is linked to tobacco smoke exposure.

Eur J Cancer Prev. 2005 Jun;14(3):223-30.

Polymorphisms in the promoter region of neutrophil elastase gene and lung cancer risk. *Park JY, Chen L, Lee J, Sellers T, Tockman MS.,* Division of Cancer Prevention and Control, Department of Interdisciplinary Oncology, H. Lee Moffitt Cancer Center and Research Institute, 12902 Magnolia Drive, MRC3047A, Tampa, FL 33612, USA. parkj@moffitt.usf.edu

The neutrophil elastase (NE) gene encodes a powerful serine protease that is involved in the process of normal tissue turnover, natural host defense or tissue damage in acute and chronic inflammatory disorders. Furthermore, NE was suggested as one of the determinant factors of individual susceptibility to lung cancer resulting from imbalance between alpha1-antitrypsin (AT) and NE. To determine whether NE plays a role in risk for lung cancer, we screened polymorphisms in the promoter region of the NE gene and assessed the role of the NE polymorphisms in the risk for lung cancer. We confirmed three previously identified polymorphisms which are located at -903, -741, and extra 52 bp STS relative to the transcription initiation site. In addition, two new polymorphisms at -832 (G/T) and -789 (C/T) were identified. Their rare allelic frequencies of new polymorphism are 0.02 and 0.01, respectively, among Caucasians. The prevalence of the NE -903 (T/T) and (T/G) genotypes were 0.88 and 0.12 in controls as compared to 0.96 and 0.04 in lung cancer patients using genomic DNA isolated from 113 Caucasian lung cancer cases and 131 controls. A significant increase in lung cancer risk was observed for expected high NE activity genotypes (OR=3.2, 95% CI=1.02-10.3) as compared to low NE activity genotypes. These results were consistent with previous in vitro functional analysis, which reported an approximately two-fold increase enzyme expression with the -903T/-741G allele as compared to the -903G/-741A variant. These results confirm that the NE promoter region polymorphisms may influence in risk for lung cancer.

Lung Cancer. 2005 Jun;48(3):315-21. Epub 2005 Jan 20.

Polymorphisms for microsomal epoxide hydrolase and genetic susceptibility to COPD. *Park JY, Chen L, Wadhwa N, Tockman MS.* Division of Cancer Prevention and Control, Molecular Screening Section, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL 33612, USA. parkj@moffitt.usf.edu

Although smoking is the major causal factor in the development of chronic obstructive pulmonary disease (COPD), only 10-20% of chronic heavy cigarette smokers develop symptomatic COPD, which suggests the presence of genetic susceptibility. The human microsomal epoxide hydrolase (EH) is a metabolizing enzyme which involves the process of numerous reactive epoxide intermediates and contains polymorphic alleles which are associated with altered EH activity and may be linked to increased risk for COPD. To determine whether the EH polymorphisms contributed to increased risk for COPD, prevalence of the EH codons 113 and 139 polymorphisms were compared between COPD patients and controls by a PCR-RFLP analysis using genomic DNA isolated from 131 COPD patients and 262 individually matched controls by age (+/-5 years) among Caucasians with 2:1 ratio. Significantly increased risk for COPD was observed for subjects with the EH(113His/His) genotypes (OR=2.4, 95% CI=1.1-5.1). These results were consistent with the fact that a significant trend towards increased risk was observed with predicted less protective EH codon 113 genotypes (p=0.03, trend test). A similar association was not observed for EH codon 139 polymorphism. As expected, a significant correlation between smoking dose and severity of COPD was observed ($p<0.001$). These results suggest that EH codon 113 polymorphism may modify risk for COPD.

Int J Mol Med. 2005 Mar;15(3):443-8.

•**African-American Families with Inherited Breast or Ovarian Cancer**
(Rebecca Sutphen, M.D.)

Recent publications:

BRCA1 and BRCA2 mutations in a Study of African American Breast Cancer Patients. *Pal T, Permuth-Wey J, Holtje T, Sutphen R.* Lifetime Cancer Screening and Prevention Center, H. Lee Moffitt Cancer Center and Research Institute, 4117 East Fowler Avenue, Tampa, FL 33617, USA.

The spectrum of mutations in BRCA1 and BRCA2 among African Americans has not been well characterized because most studies to date have been done in Caucasian families. According to Myriad Genetic Laboratories, Inc., only approximately 3% of individuals undergoing BRCA1/BRCA2 testing reported African American ancestry. Data from previous studies show that among African American women a greater proportion of breast cancer cases are diagnosed at age <45 years in comparison with Caucasians. Because breast cancer occurring at a young age is one of the hallmarks of high penetrance genes, the prevalence, spectrum, and effects of BRCA1/BRCA2 mutations may differ substantially between African Americans and Caucasians, and further investigation is warranted. We conducted a hospital-based study of African American breast cancer patients with early age at diagnosis (</=45 years) or family history of breast or ovarian cancer. We identified four deleterious mutations in BRCA1 or BRCA2 among the 10 families tested, of which two were novel BRCA2 mutations, one was the west African founder mutation (BRCA1 943ins10), and one was a recurrent mutation that may be a candidate for a second African American founder mutation (BRCA1 IVS13+1G>A). Our results support previous data in demonstrating that (a) the spectrum of mutations among African Americans is unique, (b) family history of breast cancer is an important predictor of hereditary cancer susceptibility among African Americans, and (c) empirical data may be useful in estimating mutation risk among African Americans.

Cancer Epidemiol Biomarkers Prev. 2004 Nov;13(11 Pt 1):1794-9.

REPORTABLE OUTCOMES:

- **Manuscripts, abstracts, presentations:**

  Nallamshetty L, Eschrich SA, Cuthbertson D, Malloy J, Goldgof DB, Alexander AM, Trucco M, Ilonen J, Akerblom HK, Krischer JP, TRIGR Study Group: An Expert System for Evaluating Risk of Type-1 Diabetes. *In Proceedings of the 2003 IEEE International Conference on Systems, Man and Cybernetics* 1660-1665, 2003.

  Sutphen R, Xu Y, Wilbanks GD, Fiorica J, Grendys EC Jr, LaPolla JP, Arango H, Hoffman MS, Martino M, Wakeley K, Griffin D, Blanco RW, Cantor AB, Xiao YJ,

Krischer JP: Lysophospholipids are Potential Biomarkers of Ovarian Cancer. *Cancer Epidemiol Biomarkers Prevention* 13(7):1185-1191, 2004.

Robert A. Clark, M.D., Todd Hazelton, M.D., Lynn Coppage, M.D., Thomas N. Chirikos, Ph.D., Frank Walsh, M.D., Mark Rolfe, M.D., Lary Robinson, M.D., Eric Sommers, M.D. , Nina R. Wadhwa, M.S.P.H., Gerold Bepler, M.D., Jeffrey Krischer, Ph.D. , Melvyn Tockman, M.D., Ph.D. Lung Cancer Screening with Computed Tomography: initial results of a cohort screening trial, Submitted *Radiology*.

Melvyn S. Tockman. Improbable Estimate of Lung Cancer Mortality from Screening Trials, *Journal of Clinical Oncology*, Vol 23, No 9 (March 20), 2005: pp. 2106-a-2107.

Park JY, Chen L, Elahi A, Lazarus P, Tockman MS. Genetic Analysis of Microsomal Epoxide Hydrolase Gene and Its Association with Lung Cancer Risk. Eur J Cancer Prev. 2005 Jun;14(3):223-30.

Park JY, Chen L, Lee J, Sellers T, Tockman MS. Polymorphisms in the Promoter Region of Neutrophil Elastase Gene and Lung Cancer Risk. Lung Cancer. 2005 Jun;48(3):315-21. Epub 2005 Jan 20.

Park JY, Chen L, Wadhwa N, Tockman MS. Polymorphisms for Microsomal Epoxide Hydrolase and Genetic Susceptibility to COPD. Int J Mol Med. 2005 Mar;15(3):443-8.

Pal T, Permuth-Wey J, Holtje T, Sutphen R.BRCA1 and BRCA2 Mutations in a Study of African American Breast Cancer Patients. Cancer Epidemiol Biomarkers Prev. 2004 Nov; 13(11 Pt 1):1794-9.

Gerold Bepler, Dawn Goodridge Carney, Benjamin Djulbegovic, Robert A. Clark, and Melvyn Tockman., A Systematic Review and Lessons Learned From Early Lung Cancer Detection Trials Using Low-Dose Computed Tomography of the Chest, Cancer Control 4:306-314, 2003.

- **Patents and licenses applied for and/or issued:**

Development of the Moffitt Cancer Network

A notice of disclosure has been filed with the USF office of patents in anticipation of the completion of a patent application.

- **Funding received based on work supported by this award:**

The Data and Technology Coordinating Center for the NIH Rare Disease Network (PI: Jeffrey Krischer, Ph.D.)

The Data Coordinating Center for the Study of the Environmental Determinants of Diabetes in the Young. (PI: Jeffrey Krischer, Ph.D.)

Moffitt Community Clinical Oncology Program Research Base (PI: Jeffrey Krischer, Ph.D.)

CONCLUSIONS:

The Advanced Cancer Detection Center continues to be successful. Some projects originated under the previous funding (DAMD17-98-1-8659) have been completed under the auspices of this award and others are continuing. The research has led to publications, presentations and successful grant applications. All projects have been approved for human subjects both at the University of South Florida Institutional Review Board and at the DoD Human Subjects Review Committee.

The Advanced Cancer Detection Center has been successful in developing and implementing a variety of leading edge technologies over the past five years. We plan to continue developing new technologies as well as extending existing technologies that contributes to the improvement in quality of overall patient care and public health.

REFERENCES:

References pertinent to the individual projects are contained in the appended material.

Gary Ernest Smith. *Blue Shadows.* Oil on canvas, 16″ × 20″. Courtesy of Raymond E. Johnson's Overland Gallery of Fine Art, Scottsdale, Arizona.

The potential place of computed tomography as a tool for improving lung cancer outcomes is reviewed.

A Systematic Review and Lessons Learned From Early Lung Cancer Detection Trials Using Low-Dose Computed Tomography of the Chest

Gerold Bepler, MD, PhD, Dawn Goodridge Carney, MSPH, Benjamin Djulbegovic, MD, PhD, Robert A. Clark, MD, MBA, and Melvyn Tockman, MD, PhD

Background: *Computed tomography (CT) screening of the chest has shown promise for early detection of lung cancer, but evidence for a reduction in lung cancer mortality by CT screening is not available.*

Methods: *We reviewed 208 articles to synthesize available evidence for efficacy of CT screening in detecting potentially curative stages of lung cancer and for evidence in reducing lung cancer mortality. Other outcomes of interest included detection rate of cancer and of suspicious lesions, histology and stage of cancer at detection, screening-related morbidity, and the identification of populations uniquely suited for CT screening. We identified eight papers that reported the outcomes for CT of the chest in lung cancer screening.*

Results: *Since none of the studies utilized a control group, quantitative pooling was not done. In two studies, both CT and chest radiography (CXR) were used as screening tools in the same cohorts. A total of 19,107 subjects were screened using CT. The detected prevalence rate for lung cancer ranged from 0.40% to 13.6% and was a function of the subjects' age and smoking history. CT screening resulted in a 3-fold higher detection rate and a 5-fold increase in the rate of resectable cancers compared to CXR. Data on lung cancer and overall mortality and screening-related morbidity and mortality were incomplete. CT screening resulted in selective detection of adenocarcinomas with an approximately 2- to 3-fold oversampling of this histologic subtype. The positive predictive value of CT screening was highest for subjects in the 8th decade of life, and it was virtually nil for those in their 5th decade.*

Conclusions: *Evidence regarding lung cancer screening by CT shows that this technology detects earlier-stage and smaller lung cancers with greater frequency than other screening methods. To date, no trials have demonstrated that CT screening leads to a reduction in lung cancer mortality. Until mortality trials are completed, low-dose CT screening should be considered an investigative tool rather than the standard of care.*

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No significant relationship exists between the authors and the companies/organizations whose products or services are referenced in this article.

Introduction

Lung cancer accounts for one third of cancer deaths in men and one fourth of cancer deaths in women in the United States, despite advances in the treatment and prevention of this disease.[1] The disease-specific mortality is declining in most age groups, except in women 65 to 74 years of age, where death rates continue to rise.[2] Without the development of efficacious primary prevention, the number of people diagnosed with lung cancer is expected to double in the next 50 years. Former smokers maintain lung cancer incidence rates that are greater than comparable never smokers, and these rates will increase substantially as they age.

Lung cancer treatment and survival are functions of disease stage at presentation. As stage I and II tumors rarely cause symptoms, the disease is usually diagnosed in advanced stages (stage III and IV) when potentially curative therapy is often beyond the reach of physicians' present capabilities. As a result, the overall 5-year lung cancer survival rate is only 14%, with 22% to 67% for stage I and II lung cancer and 1% to 25% for advanced stages.[3] Based on these survival results and the assumption that 5-year survival is equal to cure, the hypothesis that "early detection by screening asymptomatic individuals will result in a decline in overall and disease-specific mortality from lung cancer" has been formulated. However, none of the professional health organizations and task forces currently endorse screening for lung cancer with radiologic imaging techniques. This is a result of 3 large randomized trials that were conducted in the United States and Europe between 1960 and 1980.[4-6] These trials used frequent (every 4 to 6 months for 3 to 6 years) two-dimensional chest radiography (CXR) as a screening tool, and details are provided in Table 1. Cancers were detected at earlier stages, more cancers were resectable, and 5-year survival rates were significantly better in the screened groups compared to the control groups. However, mortality rates from lung cancer, overall mortality, and the number of unresectable cases were not significantly reduced on final evaluation. These results may be explained by lead-time bias, length-time bias, overdiagnosis, and the finding that many people in the "control group" actually had frequent CXR, which may have skewed the controls toward relatively early diagnosis of lung cancer. The impact of these biases has been explained, reviewed, and discussed elsewhere.[7-9]

Computed tomography (CT) of the chest has been reported to be superior to CXR in detecting pulmonary nodules.[10] This implies that an increase in the detection rate of putatively surgically curable lung cancers and a concomitant decline in incurable late-stage disease (ie, a stage shift) as a result of CT screening should lead to a decline in lung cancer-specific mortality, which is the ultimate goal of all early detection trials. However, whether CT screening will result in a reduction of lung cancer mortality is not known. The question of CT screening efficacy is paramount, since at least one economic analysis has shown that screening with CT is cost-effective compared to other methods of screening for lung cancer.[11] However, a recent decision

Table 1. — Summary of Eligibility Criteria and Results From Lung Cancer Screening Trials With Chest Radiography

Reference	No. of Patients	Sex	Age	Exposure (Cigarette Smoking Active or Past)	Detected Cases of Lung Cancer on Prevalence Screen	Operable Cases on Prevalence Screen	Lung Cancer Mortality in Screened Group	Lung Cancer Mortality in Control Group	Overall Mortality in Screened Group	Overall Mortality in Control Group
Brett[4] (1968)	55,034 (29,416*)	M=100%	≥40	88% PY = NS	51 (0.09%)	31 (0.06%)	N=82 (0.28%) at 3 years of follow-up	N=68 (0.27%) at 3 years of follow-up	NS	NS
Fontana[5] (1986)	10,933 (4,618*)	M=100%	≥45	100% PY = NS	74 (0.68%)**	33 (0.30%)	N=122 (2.64%) 3 years of median follow-up	N=115 (1.82%) 3 years of median follow-up	24.8% per 1,000 person-years	24.6% per 1,000 person-years
Kubik[6] (1986)	6,364 (3,171*)	M=100%	≥40	100% (all active) ≥20 PY	19 (0.30%)	NS	N=85 (2.68%) ≥5 years of follow-up	N=67 (2.10%) ≥5 years of follow-up	N=341 (10.75%) ≥5 years of follow-up	N=293 (9.18%) ≥5 years of follow-up

* Number of subjects in the screening cohort.
** Cases detected by chest radiography; cases detected by sputum cytology only are excluded (N=17).
PY = pack-years (number of packs of cigarettes smoked per day multiplied by the number of years smoked)
NS = not specified

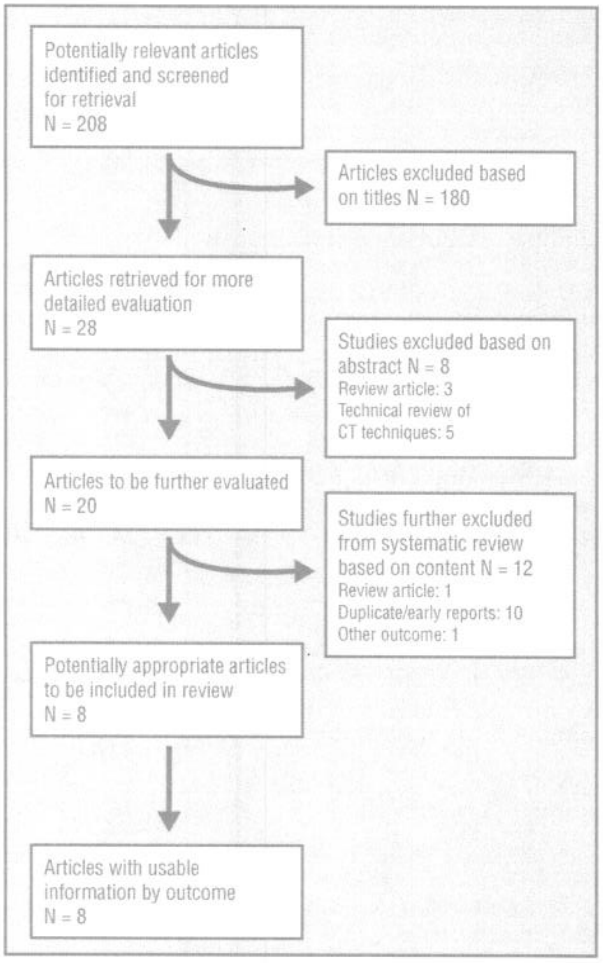
and economic analysis has suggested that the incremental cost-effectiveness associated with screening a population of current and former smokers over the age of 60 years is between $116,300 and $2,322,700 per quality-adjusted life-year gained.[12]

We have undertaken a systematic review of available studies to obtain evidence if screening by CT is able to (1) detect smaller cancers than traditional screening methods, (2) determine whether shifting the distribution toward earlier stage at detection occurs, and (3) determine if there is evidence for a decrease in lung cancer mortality.

Methods

Search Methods

Searches of MEDLINE and CancerLit databases from 1988 to August 2002 were undertaken using "lung neoplasms [MeSH] and (tomography [MeSH] OR tomography scanners, x-ray computed [MeSH]) and mass screening [MeSH]" as the search terms. The bibliographies of selected references were also searched.



Flow diagram of search results.

Study Selection

All observational studies and randomized, controlled trials (RCTs) of screening vs no screening with chest CT were eligible for this review. Studies utilizing screening via CT vs some other screening method or no screening at all were eligible for inclusion. For the RCTs, any method of randomization was eligible. Trials of screening alone and screening followed by treatment were also included. Papers were not excluded based on language. A flow diagram of the search strategy is illustrated in the Figure. Initially, 208 articles were identified for possible retrieval. After further review, we excluded 200 articles that were review articles containing no primary data, duplicate studies, preliminary reports later available as full reports, or technical reviews of methods. Eight papers published as full reports were used for data extraction. The data extracted were focused on the results from prevalence screening, and the respective data variables are shown in Tables 2 and 3.

Outcomes

The main outcomes of interest were detection rate of cancer, stage of cancer at detection, and lung cancer mortality. Other outcomes of interest included detection rate of suspicious lesions, overall mortality, histology of detected cancers, as well as screening-related morbidity and surgeries. The specific assessment questions were: What is the detection rate of screening CT for lung cancer in asymptomatic individuals, what is the stage distribution of detected lung cancers, and what is the disease-specific mortality? For analysis, data were extracted from the publications and tabulated. Specific attention was given to the demographic characteristics and potential exposures of the respective cohorts studied as well as the criteria used to evaluate the CT scans and to initiate subsequent workups.

Results and Discussion

Overview

An electronic search of the literature and handsearched review of selected bibliographies resulted in 8 papers published as full reports that were used for data extraction.[13-20] None of the identified papers were randomized, controlled trials. While two of the papers used same patient comparisons with concurrent CXR as the control,[14,18] the remaining were single-arm prospective cohort studies without explicit historical controls.

The largest and smallest reported sample sizes in these studies were 7,956 and 118, respectively.[13,17] A total of 19,107 subjects were screened using CT. Overall, the reported gender distribution showed 69.6% were men and 30.4% were women. Gender was not reported for 118 subjects. The estimated median age in these studies was 60 years (range 38 to 85 years).

Table 2 itemizes the demographics and study characteristics on the 19,107 subjects who underwent lung cancer screening by CT. Except for two studies,[15,17] nearly all subjects were current or former smokers (86% to 100%). Asbestos exposure was reported in three studies,[14,16,20] and evidence for asbestos-related lung disease was a requirement for study participation in one study.[20] This is the only study in which comorbid conditions of subjects are specifically reported. The study by Matsumoto et al[13] was a pilot study to assess the feasibility of using a mobile CT scanner for early lung cancer detection in Japan. This was a small study with 118 participants and limited available information. Because of these limitations, this study is not included in the description and discussion of reported results on CT as a screening tool for lung cancer.

Detection Rate of Lung Cancer and Factors Associated With Risk

Among all studies, the detected prevalence for lung cancer using CT ranged from 0.40%[15] to 2.70%[14] (Table 3). All studies were conducted in comparable yet dis-

Table 2. — Demographics and Characteristics

Reference	No. of Patients	Sex	Age	Comorbid Conditions	Exposure	Study Design	Comment
Matsumoto[13] (1995)	118	Not available	Not available	Not available	Not available	Prospective cohort without historical control	Abstract only; a pilot study with limited information.
Henschke[14] (1999)	1,000	M = 540 F = 460	≥60 Median 67	NR	Smokers 100% ≥10 PY Median 45 PY Asbestos 14%	Prospective cohort with same patient comparison	Radiography served as control. Final results were reported in 2001.*
Sone[15] (2001)	5,483	M = 2,971 F = 2,512	≥40 Mean 64 Range 40-74	NR	Smokers or former smokers 46.1% ≥1 PY	Prospective cohort without historical control	
Diederich[16] (2002)	817	M = 588 F = 229	≥40 Median 53 Range 40-79	NR	Smokers 100% ≥20 PY Median 45 PY Range 20-166 PY Asbestos 2.4%	Prospective cohort without historical control	
Nawa[17] (2002)	7,956	M = 6,319 F = 1,637	≥50 Range 50-69	NR	Smokers or former smokers 62.1%	Prospective cohort without historical control	All participants were members of a single health insurance group.
Sobue[18] (2002)	1,611	M = 1,415 F = 196	≥40 Range 40-79	NR	Smokers or former smokers 86%	Prospective cohort with same patient comparison	Radiography served as control. All participants were members of a for-profit lung cancer screening association. Results from 1,320 participants were reported in 2000.**
Swensen[19] (2002)	1,520	M = 785 F = 735	≥50 Mean 59 Range 50-85	NR	Smokers 100% ≥20 PY Median 45 PY Range 20-230 PY	Prospective cohort without historical control	
Tiitola[20] (2002)	602	M = 591 F = 11	Mean 63 Range 38-81	Asbestosis and/or bilateral pleural plaques	Smokers 96.7% ≥10 PY Mean 24 PY Asbestos 100%	Prospective cohort/ case series without historical control	

NR = not reported
PY = pack-years
* Henschke CI, Naidich DP, Yankelevitz DF, et al. Early lung cancer action project: initial findings on repeat screenings. *Cancer.* 2001;92:153-159.
** Kaneko M, Kusumoto M, Kobayashi T, et al. Computed tomography screening for lung carcinoma in Japan. *Cancer.* 2000;89 (11 suppl):2485-2488.

tinctly unique populations. Comparable features included a relatively strong smoking history of most participants and age above 40 years. Age was a strong risk factor for lung cancer, with combined detection rates of 0.25% in the youngest participants to 1.40% in the oldest participants (Table 4). In four studies,[14,16,19,20] nearly 100% of participants were active or former smokers. In three studies,[14,16,19] the median number of pack-years smoked was 45; however, they differed in their age eligibility criteria. Henschke et al[14] required participants to be ≥60 years of age and the lung cancer detection rate was 2.70%, while Diederich et al[16] reported a detection rate of 1.35% in participants over the age of 40 years, and Swensen et al[19] reported a rate of 1.38% in participants over the age of 50 years. This illustrates that the difference in lung cancer detection rates among these three studies can be explained by the age difference in the respective cohorts. In contrast, in the study by Tiitola et al,[20] participants had a median cigarette consumption of 24 pack-years and the lung cancer detection rate was 0.40% despite the added risk of asbestos exposure. The mean age in this group was 63 years (range 38 to 81 years), which is similar to the mean age of 59 years (range 50 to 85 years) in the study by Swensen and colleagues with a lung cancer detection rate of 1.38%. This suggests that a doubling

Table 3. — Selected Outcomes Based on Prevalence Screening Results

Reference	No. of Patients	Noncalcified Pulmonary Nodules	Detected Cases of Lung Cancer	Disease Stage		Histology		Lung Cancer Mortality	Overall Mortality (including lung cancer mortality)
Matsumoto[13] (1995)	118	Any: Not available ≥5 mm: N=43 (36.4%)	16 (13.6%)	I: IIIA: NR:	N=9 N=1 N=6	Not available		Not available	Not available
Henschke[14] (1999)	1,000	Any: N=233 (23.3%) ≥5 mm: N=97 (9.7%)	27* (2.7%)	IA: IB: IIA: IIB: IIIA: IIIB:	N=22 N=1 N=1 N=0 N=2 N=1	Adeno Squamous Adeno-squamous Carcinoid	N=22 N=1 N=4 N=1	NR	NR
Sone[15] (2001)	5,483	Any: N=279 (5.1%) ≥3 mm: N=170 (3.1%)	22** (0.4%)	IA: IB II: III:	N=21 N=2 N=0 N=0	Adeno Squamous	N=19 N=4	N=1	N=2
Diederich[16] (2002)	817	Any: N=409 (50.1%) >5 mm: N=154 (18.8%)	11* (1.35%)	IA: IB: IIA: IIB: IIIA: IIIB:	N=5 N=1 N=1 N=1 N=2 N=1	Adeno Squamous Small cell	N=6 N=4 N=1	N=3 at 2-40 months of follow-up	N=4 at 2-40 months of follow-up
Nawa[17] (2002)	7,956	Any: N=2,099 (26.4%) ≥8 mm: N=541 (6.8%)	36* (0.45%)	IA: IB: IIA: IIB: IIIA:	N=28 N=3 N=3 N=1 N=1	Adeno Large cell Carcinoid	N=35 N=1 N=1	NR	NR
Sobue[18] (2002)	1,611	Any: N=186 (11.5%) ≥5 mm: NR	13** (0.81%)	IB: IA: IIIA: IIIB:	N=1 N=9 N=2 N=1	Adeno Squamous	N=10 N=3	NR	NR
Swensen[19] (2002)	1,520	Any: N=782 (51.4%) ≥4 mm: N=475 (31.3%)	21** (1.38%)	IA: IB: IIA: IIB: IIIA: Limited:	N=13 N=1 N=4 N=0 N=2 N=2	Adeno Squamous Large cell Small cell	N=15 N=4 N=1 N=2	N=1 at 1 year of follow-up	N=9 at 1 year of follow-up
Tiitola[20] (2002)	602	Any: N=111 (18.4%) ≥5 mm: N=48 (8.0%)	5 (0.83%)	I: IIA: IIIB: IV:	N=0 N=1 N=2 N=2	Adeno Squamous Large cell "Cancer"	N=2 N=1 N=1 N=1	N=6-7 at 2.5 years of follow-up	NR

* One patient had 2 primary lung cancers.
** One additional case was discovered by sputum cytology only.
NR = not reported

Table 4. — Prevalence Rate of Lung Cancer (LC) by Age Group and Lung Cancer Risk

Age	Sobue[18] No. LC / No. Screened	Sone[15] No. LC / No. Screened	Diederich[16] No. LC / No. Screened	Nawa[17] No. LC / No. Screened	Combined No. LC / No. Screened	Relative Lung Cancer Risk*
40-49	0 / 258	2 / 238	0 / 298	NA / NA	2 / 794 (0.25%)	1.0
50-59	2 / 521	5 / 771	3 / 313	27 / 6082	37 / 7687 (0.48%)	1.9
60-69	9 / 630	9 / 1474	7 / 167	9 / 1874	34 / 4145 (0.82%)	3.3
70-79	3 / 202	7 / 471	0 / 39	NA / NA	10 / 712 (1.40%)	5.6

* The relative risk for lung cancer by age groups is provided by comparing the frequency of CT screening-detected lung cancers in age group 40-49 years with those in the older age groups. Studies that did not specifically report detection rates by age decades are not listed.

in cigarette consumption (24 to 45 pack-years) is associated with a 2- to 3-fold increase in lung cancer risk. This assumption is underlined by the studies of Sone et al[15] and Sobue et al.[18] In the former study, 46% of participants were smokers and the lung cancer detection rate was 0.40%, while in the latter study, 86% were smokers and the detection rate was 0.81%. None of the studies provided data on the amount of cigarettes smoked per day, the smoking duration, and the age of first smoking of participants. Thus a more detailed analysis on the impact of smoking behavior on CT-detected lung cancer prevalence rates in asymptomatic individuals is not possible. The relative contribution of gender to lung cancer risk cannot be assessed from the studies reviewed, although it appears that women were at an equal or perhaps slightly increased risk for lung cancer,[15,17] which is consistent with numerous epidemiologic reports.[21] It can thus be concluded that the detected lung cancer prevalence in asymptomatic individuals is a function of participants' age and smoking history.

Detection Rate of Lung Cancer on CT and CXR

Two studies[14,18] found that when comparing low-dose CT with CXR, CT screening detected more lung cancers (27 by CT vs 7 by CXR in one study, and 13 by CT vs 5 by CXR in the second). The prevalence detection rates for CXR (0.70% and 0.31%) are equivalent to those reported from the randomized lung cancer screening trials in comparable study populations conducted in the 1970s[5] and 1980s[6] of 0.68% and 0.30%, respectively. These comparable prevalence detection rates by CXR in studies that are two decades apart is remarkable, given the advances in radiography equipment and the shift in lung cancer histology from squamous cell carcinoma as the most frequent subtype in the 1970s to adenocarcinoma as the most frequent current subtype. It can thus be concluded that screening of asymptomatic individuals for lung cancer with low-dose CT results in an approximately 3-fold higher detection rate than screening with CXR.

Stage of Cancer at Detection

With regard to stage distribution in all CT screening studies, the number of stage I or II lung cancer cases was 119, compared to 18 for stage III or IV (including small-cell lung cancer cases). The stage distribution in the screened cohorts of the previously referenced early detection trials with CXR was 155 resectable and 174 unresectable cases. A clear comparison of these data is difficult for several reasons: (1) the differences in the terms *resectable* and *unresectable* in stage I/II vs stage III/IV, (2) a change in the staging system, (3) the development of more sensitive tests to detect metastases, and (4) the frequent use of surgical staging in the recent CT screening studies. These developments have resulted in up-staging rather than down-staging of newly detected lung cancer cases. Thus, cases that might have been staged as resectable in the 1970s are more likely to have been staged as unresectable in the 1990s. In addition, two of the recent CT screening studies also used CXR screening for comparison. In these studies, the combined CT- vs CXR-detected lung cancer cases were stage I in 33 vs 7 cases, stage II in 1 vs 1 case, and stage III in 6 vs 4 cases. This suggests that the higher detection rate of lung cancers by CT compared to CXR is mainly a result of an increased number of cancers detected in stage I of the disease. It appears that the increase of cases with stage I is not accompanied by a decrease in the number of cases with inoperable stages of lung cancer. If this observation is confirmed in the ongoing and planned randomized early detection trials with CT, then it is unlikely that a decrease in lung cancer mortality will occur. A decrease in lung cancer mortality would require a stage shift in the screening detected cases, ie, a decrease in inoperable cases and an increase in operable cases. If only an increase in operable cases is observed, then an increase in lung cancer incidence will occur, likely as a result of overdiagnosis. Measurement of 5-year survival as an outcome parameter for screening trials is an insufficient parameter of screening efficacy. This is exemplified by the referenced CXR-based screening trials, where 5-year survival was increased in the screened cohorts yet not accompanied by a decrease in mortality. It can thus be concluded that screening of asymptomatic

Table 5. — Positive Predictive Value of Noncalcified Pulmonary Nodules (NCPN) for Lung Cancer by Age Group

Age	Sobue[18] No. NCPN / No. Screened	Diederich[16] No. NCPN / No. Screened	Nawa[17] No. NCPN / No. Screened	Combined No. NCPN / No. Screened	Positive Predictive Value No. LC / No. NCPN
40-49	23 / 258	134 / 298	NA / NA	157 / 556 (28.2%)	0 / 157 0.000
50-59	58 / 521	155 / 313	1566 / 6082	1779 / 6916 (25.7%)	69 / 1779 0.039
60-69	73 / 630	95 / 167	533 / 1874	701 / 2671 (26.2%)	59 / 701 0.084
70-79	32 / 202	25 / 39	NA / NA	57 / 241 (23.7%)	3 / 57 0.053

individuals for lung cancer with low-dose CT may result in an up to 5-fold increase in the rate of resectable cases compared to screening with CXR, provided that CT screening is performed on participants who are medically operable. A conclusion whether or not CT screening results in a decrease of unresectable cases of lung cancer cannot be reached at this time.

Lung Cancer Mortality and Overall Mortality

Data on disease-specific and overall mortality are provided in Table 3. These data are incomplete and do not allow for a conclusion regarding the impact of CT screening on these crucial determinants of screening efficacy. First and foremost, a clear impact of screening on mortality can come only from randomized, controlled trials such as those originally conducted to assess the efficacy of CXR. Second, the reported follow-up periods on the referenced CT screening trials are too short for a meaningful comparison with global age-adjusted lung cancer mortality data, and 5-year survival results are insufficient to show screening efficacy because of the inherent biases of such data. Third, participants in the reported CT screening trials represent special populations, and therefore the results obtained are not necessarily applicable to the population at large. Notably, the study that included asbestos workers had the highest lung cancer and overall mortality rates,[20] which can be explained by the comorbidities of the study participants. A conclusion on the efficacy of CT screening on disease-specific and overall mortality cannot be reached from the available data.

Screening-Related Morbidity and Mortality

No screening-related deaths were reported. Only one of three studies that reported surgery-related deaths incurred an actual death,[20] and there was no surgery-related morbidity or mortality reported by other studies. A conclusion on screening-related morbidity and mortality cannot be reached based on the reported results.

Histology of Detected Lung Cancers

The predominant histology of lung cancers detected in the CT screening trials was adenocarcinoma, accounting for 109 (79.6%) of the 137 lung cancers. Only 17 cases (12.4%) of squamous cell carcinoma and 11 (8.0%) of other subtypes were reported. These numbers are clearly divergent from the numbers reported in the Surveillance, Epidemiology, and End Results (SEER) database for a comparable time period (ie, lung cancer cases from 1983 to1992), where adenocarcinoma accounted for 34.9%, squamous cell carcinoma for 31.4%, and all others for 33.7% of lung cancers. This strongly suggests that CT screening as a tool for secondary prevention of lung cancer preferentially detects adenocarcinomas and may not be sufficiently sensitive to detect squamous and small-cell carcinomas. Thus, it can be concluded that CT screening as a tool for early detection of lung cancer results in over-sampling for adenocarcinomas by a factor of 2 or more.

Detection Rate of Suspicious Abnormalities (Noncalcified Pulmonary Nodules)

The rate of noncalcified pulmonary nodules (NCPNs) ranged from 5.1% to 51.4% (Table 3), and the smallest diameter of detectable lesions was below 3 mm. Thus, the positive predictive value (proportion of lung cancers among those with suspicious lesions) of CT scanning for lung cancer was variable (0.02 to 0.12). This range is comparable to that of mammography in breast cancer screening or fecal occult blood testing in colorectal cancer screening.[22,23] Neither the specificity nor the sensitivity of CT scanning for lung cancer detection can be assessed because the proportion of individuals "truly negative" for lung cancer at the time of testing is unknown. Given the discrepancy in the distribution of histologic subtypes of lung cancers detected by CT compared to those reported nationwide, it is reasonable to assume that the false-negative rate of CT scanning for lung cancer may be substantial. An estimate is reported by Sone et al[15] with a sensitivity (proportion of lung cancers determined by CT among all participants who have lung cancer) ranging from

55% to 83% and a specificity (proportion of non-lung cancers by CT among all participants who do not have lung cancer) of 95% to 97%. For obvious reasons, CT scanning will be most efficacious in populations where CT scanning provides the highest possible positive predictive value. Table 5 summarizes the available results from the reported trials. It is noteworthy that the rate of NCPNs does not increase with age after 40 years of age (column 5 in Table 5), while the lung cancer risk increases with age. As a result, the positive predictive value of CT for lung cancer detection is best for subjects over the age of 60 years (~0.08), it is low (~0.04) for subjects between 50 and 59 years, and it is vanishingly small (~0.00) for subjects less than 50 years of age. These numbers apply to populations with low or minimal comorbidity such as those found in the reported screening cohorts and for prevalence screening only.

Quality Assessment

After reviewing the articles for quality, we found that available evidence on the role of CT screening in early detection of lung cancer is limited and that the reported results may be biased. Some are as follows:

- Less than half of the articles reviewed used a broad spectrum of patients or described the selection criteria of their subjects. As a result of the differences in demographic and clinical features between populations, measures of diagnostic accuracy may be confounded by biologic differences in population disease frequency, resulting in spectrum bias.

- Most studies used consensus among readers to resolve disagreement for questionable results. However, it is unclear if the readers were blinded to patient information or to the results of other tests, thus raising the potential for review (detection) bias.[24,25]

- In many of the studies, patients received a different reference test to verify the results of the CT screen. This is likely to result in partial verification bias.[24,25]

- Finally, none of the articles addressed how withdrawals or losses to follow-up were handled in analysis, which can lead to biased estimates of test performance.[26]

Conclusions

Two decades of trials with CT scanning for secondary prevention of lung cancer have taught us many valuable lessons on how to best deploy this powerful technique. Given its exquisite sensitivity in detecting radiographic pulmonary abnormalities, CT scanning is best suited in populations with a low probability of benign pulmonary abnormalities (eg, histoplasmosis, tuberculosis, and interstitial pneumonitis). In such a population, the highest positive predictive value for lung cancer will be in persons above 60 years of age. This is exemplified by the Early Lung Cancer Action Project (ELCAP) study, which enrolled patients above the age of 60 with a history of moderate cigarette use and no other significant comorbidities (participants had to be asymptomatic and medically fit for surgery). The rate of NCPNs in this study was 23.3%, the rate of cancers was 2.7%, and the positive predictive value was 0.116, which is the highest of all reported studies. Currently available results are encouraging for a possible future utility of this method in combating lung cancer mortality. Demonstrating a longer survival is a certainty for this technology and easily explained by lead-time bias.

History has taught us a lesson; hopes were high in the 1960s, when pilot trials with CXR showed promising results akin to those described here for CT. It is our obligation as highly trained academicians and physicians to individuals at risk and to future generations to complement the CT pilot studies with definitive, prospective, unbiased, and population-wide trials in order to either accept or reject the working hypothesis that early detection of lung cancer by CT screening will reduce lung cancer mortality.

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